Neural and genetic determinants of creativity

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Abstract

Creative thinking plays a vital role in almost all aspects of human life. However, little is known about the neural and genetic mechanisms underlying creative thinking. Based on a cross-validation based predictive framework, we searched from the whole-brain connectome (34,716 functional connectivities) and whole genome data (309,996 SNPs) in two datasets (all collected by Southwest University, Chongqing) consisting of altogether 236 subjects, for a better understanding of the brain and genetic underpinning of creativity. Using the Torrance Tests of Creative Thinking score, we found that high figural creativity is mainly related ($p<10^{-20}$) to high functional connectivity between the executive control, attention, and memory retrieval networks (strong top-down effects); and to low functional connectivity between the default mode network, the ventral attention network, and the subcortical and primary sensory networks (weak bottom-up processing) in the first dataset (consisting of 138 subjects). High creativity also correlates significantly with mutations of genes coding for both excitatory and inhibitory neurotransmitters ($p<10^{-17}$). Combining the brain connectome and the genomic data we can predict an individual's creativity score 78.4%, which is significantly better than prediction using single modality data (gene or functional connectivity), indicating the importance of combining multi-modality data. Our neuroimaging prediction model built upon the first dataset was cross-validated by a completely new dataset with 98 subjects and 64.6% of an individual's creativity score was predicted. In addition, the creativity–related functional connectivity network we identified in the first dataset was still significantly correlated with the creativity score in the new dataset ($p<10^{-3}$). In summary, our research demonstrates that strong top-down control versus weak bottom-up processes underlie creativity, which is modulated by competition between the glutamate and GABA neurotransmitter systems. Our work provides the first insights into both the neural and the genetic bases of creativity.

Introduction

Creativity in humans is a complex cognitive behavior commonly defined as the ability to generate responses that are novel, useful, and appropriate, (Sternberg and Lubart, 1996). Creative thinking plays an important role in almost all aspects of our life, most prominently in the arts, science, and engineering.

Divergent thinking tests are so far the major type of psychometric instrument in creativity testing (Gardner, 1988; Plucker and Runco, 1998), including various verbal and figural tasks. Based on the divergent thinking tests, mounting evidence suggests that the default mode network and brain regions associated with cognitive control may be important for creativity. For example, regions of the default mode network, including the precuneus (Fink et al., 2014a; Fink et al., 2014b; Jauk et al., 2015; Jung et al., 2010; Takeuchi et al., 2010) and inferior parietal lobule (Takeuchi et al., 2011), and executive control network (ECN) (Ellamil et al., 2012; Gonen-Yaacovi et al., 2013) have been implicated in neuroimaging studies of divergent thinking tasks. The activation of the default mode network (DMN) in creative processes may reflect the spontaneous generation of candidate ideas, and/or the retrieval of long-term memory (Beaty et al., 2016), while the control network may serve to constrain cognition to meet specific goals of the tasks.

As a highly complex cognitive process, creativity relies on not only the activity of separate brain regions but also the interactions between different brain regions/networks (Bullmore & Sporns, 2009; Fox et al., 2005; van den Heuvel & Hulshoff Pol, 2010). Functional connectivity (the correlation between the BOLD signal of different brain regions) depicts the interaction between different brain regions, which is informative for complex behaviors such as creativity and cognition. For instance, Beaty (2014) found greater connectivity between the entire DMN and the left inferior frontal gyrus (IFG) within the ECN in highly creative individuals (Beaty et al., 2014). In addition, a recent study found that the strength of connectivity between the DMN and the frontoparietal network (FPN) was positively related to both visual and verbal creativity using independent component analysis (Zhu et al., 2017). Such findings suggest that creative thought may benefit from the cooperation of the DMN and ECN.

The genetic basis of divergent thinking has been previously explored mainly by using candidate gene approaches. Several brain regions in the dopaminergic (DA) system have been found to be involved in creativity (Flaherty, 2005; Heilman et al., 2003; Takeuchi et al., 2010). Many genes in the dopamine pathway, like D2 Dopamine Receptor (DRD2) (de Manzano et al., 2010; Reuter et al., 2006), D4 Dopamine Receptor (DRD4) (Mayseless et al., 2013), Tryptophan Hydroxylase (TPH1) (Reuter et al., 2006)， Dopamine Transporter 1 (DAT1), and Catechol-O-Methyltransferase (COMT) (Zabelina et al., 2016), were selected as candidate genes and found to be associated with divergent thinking. In addition, several psychiatric illnesses are found

to have genetic links to creativity. For example, some genes involved in the pathology of psychosis, such as neuregulin 1 (NRG1), are also associated with creativity (Keri, 2009).

Although previous studies have explored the relationship between brain networks and creativity, most studies have focused on the regions previously implicated in creativity (ROI-based), or used correlation analysis, i.e., correlation between neuroimaging metrics and behavioral scores, to search for the neural basis of creativity (correlation-based). One the one hand, the ROI-based analysis may limit the potential search to only a small part of the whole brain, thus precluding the possibility of new findings. On the other hand, correlation-based approaches have the disadvantage that they tend to overfit the data and often fail to generalize to novel data (Shen et al., 2017). In addition, although several studies have explored creativity-related candidate genes, a search for the genetic basis of creativity at a genome-wide scale, especially for divergent thinking, has not been described as far as we know.

Based on all the above, in the present study we used a large sample of 236 individuals (which we separated into two non-overlapping datasets) in this research, which enabled statistical analyses of whole-brain functional connectivity links (34,716 functional connectivities) and whole-genome genes (309,996 SNPs) that were related to creativity without a priori hypotheses, therefore not creating constraints on the brain regions and genes to be investigated. Furthermore, we used a cross-validation based approach to identify the functional brain networks that are predictive of creativity, to ensure that the results were statistically firm and could be generalized to new populations. Our approach is improved from one that has been used to predict sustained attention in resting-state fMRI (Rosenberg et al., 2016) by modifying their method to deal with multi-modal data. The prediction-based approach is held to provide fMRI-derived statistics that relate to individual behaviors with more generalizability than traditional correlation-based analysis (Dubois and Adolphs, 2016). Furthermore, to understand the genetic underpinning of creative thinking, we also searched from the whole genome the SNPs (single nucleotide polymorphisms) whose mutations correlate most closely with the creativity score using the same prediction-based strategy. Part of the aim here was to investigate how multi-modal data (in this case fMRI and genetic data) can be combined, and whether this helps better predictions to be made. This research provides the first whole-brain functional network analysis for creativity with a corresponding whole-genome search for related SNPs, and is aimed to shed light on both the neural and genetic underpinnings of creative thinking.

Materials and Methods

Data

Ethics Statement

Both the behavioral and MRI protocols were approved by the local ethics committee of Southwest China University, Chongqing. Written informed consent was obtained from all participants prior to the study, which was approved by the Institutional Human Participants Review Board of Southwest University Imaging Center for Brain Research. The methods were conducted in accordance with approved guidelines.

Participants

Three hundred and fifteen subjects were recruited in this study (Li et al., 2016). We firstly excluded 63 subjects without complete behavioral or other demographic data. After further fMRI head movement control, 236 subjects were retained for further analysis. The retained subjects were then divided into two datasets. The first dataset consisted of 138 individuals, 49 males and 89 females (age 19.7 ± 1.2 (mean ± sd)), with both genetic and neuroimaging data, which we used to perform our multimodal prediction analysis. The second dataset consisted of 98 individuals, 38 males and 60 females (age 20.2 ± 1.3 (mean ± sd)), with neuroimaging data, which we used as an external validation dataset to validate our prediction model using the neuroimaging data.

All the resting-state fMRI data were collected in the Southwest University Center for Brain Imaging, Chongqing, China, using a 3.0-T Siemens Trio MRI scanner (Siemens Medical, Erlangen, Germany). Each subject was required not to drink alcohol the day before the experiments, which was then confirmed right before the scanning by questionnaires.

Resting-state fMRI

In resting-state fMRI scanning, the subjects were instructed to rest without thinking about a particular topic, and not to fall asleep or close their eyes. The 8-min scan of 242 contiguous whole-brain resting-state functional images was obtained using gradient-echo planar imaging (EPI) sequences with the following parameters: slices = 32, repetition time (TR)/echo time (TE) = 2000/30 ms, flip angle = 90, field of view (FOV) = 220 mm × 220 mm, and thickness/slice gap = 3/1 mm, voxel size $3.4 \times 3.4 \times 3$ mm^3.

Structural MRI

A magnetization-prepared rapid gradient echo (MPRAGE) sequence was used to acquire high-resolution T1-weighted anatomical images (repetition time = 1,900 ms, echo time =2.52 ms, inversion time = 900 ms, flip angle = 90 degrees, resolution matrix = 256 × 256, slices = 176, thickness =1.0 mm, voxel size = $1 \times 1 \times 1 mm^3$).

Creativity assessment

We adopted the **Torrance Tests of Creative Thinking** (TTCT) score that measures divergent thinking, which is a central aspect of creativity (Huang et al., 2013; Sternberg and O'HARA, 1999). The TTCT contains verbal, figural and auditory tests (Huang et al., 2013). The Figural TTCT is supposed to be less biased than the verbal TTCT test (Kim KH 2006), and thus is the focus of this paper. The figural test comprises of 3 tasks: picture construction, picture completion, and lines. To be specific, all the participants answer the same questions with a ten-minute time limit for each task. The first activity requires subjects to draw a picture based on an ellipse shape provided on the page. The second activity requires subjects to use 10 incomplete figures to make an object or picture. The third activity requires subjects to draw as many as possible pictures or objects on three pages of vertical lines. Participants were told to draw as many as possible and as creatively as possible.

For each task the scoring comprised three components: fluency (the number of meaningful and relevant responses, which is associated with the ability to generate and consider other possibilities), flexibility (the number of different categories of responses, which reflects the ability to shift between conceptual fields), and originality (the degree of originality of the responses, which is associated with thinking "outside the box") (Chavez-Eakle et al., 2007). More specifically, the score of fluency is the number of meaningful responses, the score of flexibility is the number of different categories of response, and the score of originality is the degree of originality of the response with a four-point rating scale ranging from 0 ("not original") to 3 ("highly original").

Three trained raters took part in the scoring. The raters displayed high internal consistency in their ratings (Cronbach alpha = 0.90). The current study used the total creativity scores (sum of the fluency, flexibility and originality scores) (de Souza et al., 2010) for each dimension which was highly correlated with the fluency, flexibility and originality scores (details in **Fig. S1**) on the basis of the findings of Heausler and Thompson (1988), who suggested that because of the high correlations between the three subscales of the TTCT the subscales do not provide meaningfully different data (Heausler and Thompson, 1988).

General intelligence assessment

The participants' intellectual ability was examined using the Combined Raven's Test (CRT). As the test is a highly reliable and valid intelligence test, it is widely used (Tang et al., 2012). In our study, all the 138 participants completed the test with the 72 items, including the Raven's standard progressive matrix (C, D, E sets) and Raven's colored progressive matrix (A, AB, B sets), revised by the Psychology Department of East China Normal University in 1989. The total number of correct answers that an individual presented in 40 minutes was used as a psychometric index of individual intelligence (Jaeggi et al., 2008).

Genotyping

Among all the participantes in our study, 138 individuals were genotyped by using the DNA samples extracted from their whole blood. For each sample, approximately 200 ng of genomic DNA was used to genotype on the Human Omni-Zhonghua chips (Illumina, San Diego, CA, USA). All samples were processed following the Illumina Infinium assay manual. Briefly, each sample was whole-genome amplified, fragmented, precipitated, and resuspended in an appropriate hybridization buffer. Denatured samples were hybridized on a prepared Human Omni-Zhonghua chip for a minimum of 16 hours at 48ºC. Following hybridization, the beadchips were processed for the single-base extension reaction, stained, and imaged on the iScan Reader (Illumina, Inc.). The Illumina iScan uses a laser to excite the red and green fluorophores attached at the single-base primer extension and staining steps. The laser-scanner records high resolution images of the light emitted by the excited fluorophores. The raw intensity data from these images is stored in ‘‘idat” files which are used for analysis on the GenomeStudio software genotyping module. Normalized bead intensity data were obtained for each sample after being loaded into the GenomeStudio software (Illumina, Inc.), which then converted fluorescent intensities into SNP genotypes. SNP clusters for genotype calling were examined for all SNPs using the GenomeStudio software. For quality control, only SNPs that were genotyped in more than 98% of samples were included in the further analysis, and SNPs that met over 0.97 of the call rate were retained.

Method

FMRI data preprocessing

All fMRI data were preprocessed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm) and the Data Processing Assistant for Resting-State fMRI (DPARSF) (Chao-Gan and Yu-Feng, 2010). We first discarded the first 10 EPI scans to suppress the equilibration effects and the remaining scans were slice timing corrected, realigned and normalized to a standard template (Montreal Neurological Institute) based on T1 images using linear transformation and resampled to $3 \times 3 \times 3$ mm^3. Next, spatial smoothing (8 mm Full Width Half Maximum FWHM), band-pass temporal filtering (0.01-0.1Hz), nuisance signal removal from the ventricles and deep white matter, global mean signal removal, and 24 head motion correction parameters (Friston et al., 1996) were involved to remove the sources of spurious correlations. We also implemented additional careful volume censoring (“scrubbing”) movement correction suggested by Power et. al. (Power et al., 2014) to remove the head-motion artifacts. The mean framewise displacement (FD) was computed with FD threshold for displacement being 0.2 mm. In addition to the frame corresponding to the displaced time point, 1 preceding and 2 succeeding time points were also deleted to reduce the ‘spill-over’ effect of head movements. Subjects with >10% displaced frames flagged were excluded from the

analysis as it is likely that such high-level of movement would have had an influence on several volumes.

SNP quality control

Single-nucleotide polymorphisms (SNPs) with call rate < 95%, minor allele frequency <5%, or deviation from the Hardy-Weinberg equilibrium with $p < 10^{-6}$, were excluded from the analysis. Individual samples showing an over- or under abundance of heterozygosity (>5 s.d from the mean) were excluded from the subsequent analysis. In order to prevent collinearity between SNPs, we further excluded SNPs in strong linkage disequilibrium ($R^2 > 0.9$) within a window of 50 SNPs using the --indep command implemented in PLINK. Finally, after quality control, we obtained 309,996 SNPs in the 138 participates.

Whole-brain functional network construction

A 264 putative functional area template that Power and colleagues defined was used to identify nodes in the whole-brain network (Power et al., 2011). Their 264-region network definition has been shown to perform better than the 90-parcel AAL atlas and voxel-based graph in representing some aspects of the functional organization of the brain with fMRI data (Power et al., 2011). The 264 regional time series were extracted by averaging voxel time series within each ROI. Then, for each subject, the Pearson cross-correlation between all pairs of regional BOLD signals was calculated to reflect the functional connectivity between region pairs. A brain network consisting of the 264 brain regions and 34,716 functional connectivity links that connected them was constructed.

Creativity-related functional brain network strength

We used a procedure similar to that presented by Rosenberg et. al. (Rosenberg et al., 2016) to construct the functional brain network closely related to the TTCT figural score and then calculate the network strength. We first calculated the Pearson correlation between each of the 34,716 (in the 264 nodes network) functional connectivity links and the score with the age, sex, and the Raven's score being covariates of interest across all subjects. Then, the functional connectivities whose p-value was smaller than a predefined threshold ($p_{threshold}$) were selected, which were further separated into those with functional connectivity positively-related and negatively-related to the figural TTCT score. Since these individual functional connectivity links always share common nodes (brain regions), we call a set of such connectivity links a network. For example, the functional connectivities that were significantly positively/ negatively related to the TTCT score comprise the positively-related/ negatively-related network, and all functional connectivity links that were significantly related to the figural TTCT score comprise the overall network. The sum of all FCs in the corresponding networks was defined as the network strength.

Creativity-related polygenic alliance

In order to identify SNPs that were significantly related to the TTCT score, we used a linear regression model with the TTCT score being the phenotype and age, sex and the Raven's score as covariates. Similar to the identification of the creativity-related functional brain network, we chose SNPs whose mutations correlated with the TTCT score significantly (p-value smaller than the $p_{threshold}$), and then divided them into the positive and the negative group (according to their correlation with the TTCT score). Then, the sum of the mutation states (0, 1, 2) of all the SNPs in the positively-related polygenic alliance, negative-related polygenic alliance, and the whole polygenic alliance, were defined as the mutation strengths, respectively.

Predicting creativity by brain connectome or genome

A leave-one-out cross-validation approach was then adopted to predict the TTCT score of novel individuals, as follows, using the network strength of the creativity-related brain networks or the mutation strength of the polygenic alliances and other covariances as predictors (see **Fig. 1** for details).

For each modality of data, we changed the $p_{threshold}$ (0.0001, 0.0005, and 0.001 to 0.01 with a step of 0.0005). For a given $p_{threshold}$, we performed the leave-one-out cross-validation approach n times (n=number of subjects), each time with one subject being the test set, and the rest of the subjects were used to construct the creativity-related brain networks or the polygenic alliances. The creativity-related network strength or the mutation strength were calculated for individuals in the training set and then fed into the linear regression models for prediction. We used four kinds of prediction model with 1. the positive network/mutation strength, 2. negative network /mutation strength, 3. overall network/mutation strength and 4. the positive network/mutation strength and the negative/mutation strength, being used respectively in each model. The age, sex, and the Raven's score were included in all the four models as covariance terms. Then, the remaining test subject, who was not used in the construction of the prediction models, was employed to test all 4 models to achieve the best prediction of the TTCT score. The goodness of prediction was assessed by the correlation between the predicted and real TTCT score. The optimal $p_{threshold}$ and final regression model were the ones with the best prediction.

Prediction of TTCT score combining multi-modal data

After we determined the optimal model and $p_{threshold}$ for prediction of creativity for the neuroimaging and genetic data, respectively, we then combined these two modalities using the elastic net linear regression model to predict the creativity score of individuals (Zou and Hastie, 2005). The elastic regression model was used here because the neuroimaging and genetic data may be highly correlated. This model involved the network strength, the mutation strength, age, sex and the Raven's score as predictors.

The network strength and the mutation strength were determined by the optimal prediction model identified in single modality data. The details of the regression model we used are as follows:

$$Y = \beta_0 + \sum_i \beta_{1i} S_i + \sum_j \beta_{2j} T_j + \sum_k \beta_{3k} C_k + \varepsilon \quad (1)$$

where *Y* is the TTCT figural score, S_i is the ith network strength we used in the best brain connectome prediction model, T_j is the jth mutation strength we used in the best genome prediction model, C_k is the kth covariance (age, sex or Raven's score) , ε is the noise term, and $\beta_{0,}$ β_{1i}, and β_{2j} are determined by the elastic-net approach that solves the following problem:

$$\min_{\beta}\left(\frac{1}{2(N-1)}\sum_{n=1}^{N-1}\left(y^{(n)} - \beta_0 - \sum_i \beta_{1i} s_i^{(n)} - \sum_j \beta_{2j} t_j^{(n)} - \sum_j \beta_{3j} c_j^{(n)}\right)^2 + \lambda P_\alpha(\beta)\right) \quad (2)$$

where N is the number of samples, $y^{(n)}$, $s^{(n)}$,$t^{(n)}$ and $c^{(n)}$ represent the TTCT score, the network strength, the mutation strength and the covariance of the nth sample, $\beta = (\beta_0, \beta_{11}, \cdots, \beta_{21}, \cdots, \beta_{31}, \cdots)$

$$P_\alpha(\beta) = \sum_{k=0,11,\cdots 21,\cdots 31,\cdots}\left[\frac{(1-\alpha)}{2}{\beta_k}^2 + \alpha|\beta_k|\right] \quad (3)$$

Finally, a leave-one-out procedure was performed again to determine the optimal α and λ (searching in [0,1] with a step of 0.01) with maximal correlation between the predicted TTCT score and the real TTCT. The final α that we used was 0.80 and the final λ was 0.66.

Permutation analysis

To determine whether the prediction result is significantly better than random, a non-parametric permutation analysis was performed. As our prediction pipeline needs hours to run, a very large number of permutations time was not realizable. So, we randomly shuffled the TTCT scores across all the 138 individuals 1000 times and ran our prediction pipeline for each permutation run. The null distribution for the correlation between the predicted scores and the real scores was obtained. Then, based on the null distribution, the p value of our prediction result was obtained.

Identification of the shared creativity network and polygenic alliance underlying creativity

In the leave-one-out prediction of the creativity score, each trial had identified a different set of FCs or SNPs. To find the FCs or SNPs that were shared among all individuals, we selected those FCs or SNPs that appeared in each leave-one-out trial. As these FCs and SNPs are related to creativity across all individuals, they may be closely related to the creativity score. Further, the Pearson correlations between the

TTCT score, the network strength of the shared creativity network, and the mutation strength of the shared polygenic score, were also calculated with the age, sex and the Raven's score as the covariance terms.

Independent validation: using the shared creativity network

We used the second dataset that consisted of 98 individuals with only fMRI data to validate our imaging prediction model. First, using all the 138 samples in group 1, a linear model for the TTCT score was constructed, using the network strength of the shared creativity network, sex, age, and Raven's score. (This network consists of links that we identified that were significantly correlated with the creativity and shared among all individuals by our predictive framework). Then, for each of the 98 individuals in group 2 the network strength (i.e. the sum of the functional connectivities of the links) of the shared creativity network identified in group 1, with their sex, age, and Raven's score, were fed into the linear model to predict the TTCT score of each individual in group 2. The Pearson correlation between the real TTCT score and the predicted TTCT score was calculated for individuals in group 2 to indicate the generalizability of our prediction model and its significance was determined by performing non-parametric permutation analysis.

Results

Prediction of the TTCT figural score

Using the whole brain functional connectome, the correlation between the TTCT score predicted by the optimal prediction model with the real TTCT score was 0.424 ($p = 2.19 \times 10^{-7}$, **Fig. 2a**). With whole genome data, the correlation between the predicted and real TTCT score was 0.466 ($p = 8.70 \times 10^{-9}$, **Fig. 2a**). The mean absolute percentage errors (MAPE) of the two prediction models were 23.9% and 22.5%, respectively (76.1% and 77.5% in terms of accuracy). With combined neuroimaging and genomic data, the correlation between the predicted TTCT score and the real TTCT score increased to 0.524 ($p = 4.33 \times 10^{-11}$), with the MAPE of the model being 21.6% (78.4% in terms of accuracy), see **Fig. 2b**. The absolute prediction error of the model that combined neuroimaging and genomic data is significantly smaller than the one that only used neuroimaging data or genetic data (one sample t-test, $p = 0.002$ and $p = 0.042$). The details of the final prediction models (the coefficients of the covariates in the linear regression model) and the optimal $p_{thresholds}$ we used can be found in the Supplementary Material. In the functional neuroimaging regression analysis, the coefficients for the neuroimaging data provided in the Supplementary Material show that the coefficient for the average network strength made a contribution to the prediction that was significant at $p=6.19\times10^{-13}$, and that the coefficients for age, gender, and the Raven's score made no significant contribution to the prediction. Thus, the predictions were being made from the neuroimaging data, and not from the

covariates of age, gender, and the Raven's score. In addition, for the prediction model using genomic data, the negative and positive mutation strength also made the main contribution to the prediction results with coefficients significant at $p=4.80\times10^{-14}$ and $p=1.34\times10^{-7}$, respectively. To ensure that our leave-one-out framework can provide results that are significantly better than random, a non-parametric permutation analysis was performed to test the significance of the correlation between our predicted TTCT scores and real scores. One thousand times of random permutation were performed and resulted in a correlation significant at $p<0.001$ (see **Fig. S2** for more details).

Creativity network and polygenic alliance shared among subjects

The TTCT-related functional connectivity links (FC) that were shared among all subjects are listed in **Table 1**, divided into positively-related (22 FCs) and negatively-related groups (60 FCs). Most positively-related FCs (12) were associated with DMN, control networks and attention networks. 4 FCs connect ROIs in different task control networks and attention networks; 3 FCs connected the frontal-parietal task control network with the visual network. Another 4 FCs contained ROIs in the default mode network (DMN), with 2 FCs within the DMN and 2 FCs connecting the DMN with the visual and ventral attention network.

For the negatively-related FCs, 20 of them were associated with the DMN, with 3 FCs within the DMN. Of the other 17 FCs associated with the DMN, 5 FCs connected with the ventral attention network, 1 with the fronto-parietal task control network, 5 with the primary sensory networks such as visual, sensory and auditory network, and another 5 with the subcortical network. In addition to default mode regions, the FCs between the control/attention networks and visual networks also correlated with creativity. There were 4 FCs connecting the cingulo-opercular task control network with the visual network and 5 FC connecting the ventral attention network and visual network.

The TTCT-related SNPs that were shared among all subjects (polygenic alliance) are listed in **Table 2**, with 5 positively related to TTCT and 8 negatively related. Specifically, SNP rs6606905 in the GABRG3 intron region was negatively correlated with the creativity score, and the corresponding gene encodes a receptor for the major inhibitory neurotransmitter GABA in the brain. SNPs rs4340077 (positively correlated with the score) is in the intron region of SHANK2, which is an adapter protein in the postsynaptic density (PSD). SHANK2 has a function in coupling glutamate receptor scaffolds to the actin cytoskeleton and intracellular signaling pathways by means of their protein-protein interaction domains (Naisbitt et al., 1999). Rs9877993, another SNP that positively related to TTCT, is in the intron region of FGF12 a member of the fibroblast growth factor family, which had also been found to be related to the excitatory neurotransmitter glutamate (Turner et al., 2012).

Correlation within/between the creativity network and polygenic alliance

The network strengths of the FCs that were positively and negatively related to TTCT (denoted by FC_pos_TTCT and FC_neg_TTCT, respectively) correlated more significantly with the TTCT score (r = 0.698, $p = 4.33 \times 10^{-21}$ for positively related FCs and r = -0.771, $p = 4.33 \times 10^{-28}$ for negatively related FCs) than the FCs between any single pair of brain regions. The mutation strength of the SNPs that are positively and negatively related to figural TTCT (denoted by SNP_pos_TTCT and SNP_neg_TTCT, respectively) were also more significantly correlated with the TTCT score (r = 0.704,$p = 5.60 \times 10^{-22}$ for positively related SNPs, and r= -0.651, $p = 5.37 \times 10^{-18}$ for negatively related SNPs) than single SNP, see **Table 1** and **Fig. 3a**.

The network strengths of FC_pos_TTCT and FC_neg_TTCT also correlated more significantly with the mutation strengths of SNP_pos_TTCT and SNP_neg_TTCT than each of the single functional connectivity, with r = 0.541, $p = 1.30 \times 10^{-10}$ between FC_pos_TTCT and SNP_pos_TTCT, r=-0.403, $p = 1.48 \times 10^{-6}$ between FC_pos_TTCT and SNP_neg_TTCT, r=-0.539, $p = 1.68 \times 10^{-11}$ between FC_neg_TTCT and SNP_pos_TTCT, and r= 0.632, $p = 8.55 \times 10^{-17}$ between FC_neg_TTCT and SNP_neg_TTCT, see **Fig. 3a**.

Independent validation results

Firstly, we used all the 138 samples in the first group to construct a linear prediction model using the shared creativity network. The neuroimaging model from the first group used the overall network strength of the shared creativity network with age, sex and Raven's score to fit the TTCT score, which was the optimal prediction model that we obtained from our leave-one-out procedure. Then, the 98 samples from the second dataset that were not used to build the model were used to independently validate the neuroimaging prediction model. The correlation between the predicted score and the real TTCT score was 0.267 (p = 0.0078), with the MAPE of the model being 35.4% (64.6% in terms of accuracy) (see **Fig. S3** for more details). A non-parametric permutation analysis was then used to determine the significance of our independent prediction results. To achieve this, we randomly permuted the real TTCT score of the 98 samples and calculated the Pearson correlation between the shifted TTCT scores and the prediction scores for 10000 times to form the null distribution. The p-value of our prediction results is 0.0032. In addition, the correlation between the network strengths of the FC_pos_TTCT and FC_neg_TTCT that we identified in the first dataset were still significantly correlated with the TTCT score in the second dataset with r= 0.284 ($p = 8.85 \times 10^{-4}$) and r= - 0.311 ($p = 2.59 \times 10^{-4}$).

Discussion

In this work, we use a cross-validation based predictive framework to search for the imaging and genetic correlates of creativity to provide more generalization than

traditional correlation analyses. We found that models using the network strength of the creativity network or the mutation strength of the creativity polygenic alliance could predict the individual's performance with high accuracy, indicating that markers for creativity are present in both the functional connectivity between brain regions and in the genetic sequence. Further, the prediction model that combined neuroimaging and genetic data achieved results significantly better than prediction with single modality data, indicating that complementary information can be provided by different modalities, in this case functional neuroimaging and genetic modalities. Combining multi-modal data helped us to obtain a fuller picture of the biological mechanisms underlying creativity. We were able to validate our neuroimaging prediction model using a completely novel group containing 98 individuals.

We used the FCs obtained from the resting-state in our analysis, which can reflect patterns similar to those in cognitive task activation studies (Biswal et al., 1995; Smith et al., 2009; Tavor et al., 2016). The FCs we identified to be related to creativity are primarily associated with the DMN and are among various higher level networks, such as the DMN, attention network and control network. These networks have all been implicated in creative thought processes (Dietrich and Kanso, 2010; Fink et al., 2014a; Fink et al., 2014b; Jung et al., 2010; Takeuchi et al., 2011; Takeuchi et al., 2010). The DMN activity is associated with internally focused mental processes, such as mind wandering, perspective-taking, episodic future thinking and autobiographical retrieval (Andrews-Hanna et al., 2014). A growing number of studies reported that the DMN was recruited to generate novel ideas in both domain-general and domain-specific creativity tasks (Liu et al., 2015; Saggar et al., 2015). For example, individual differences in brain functional connectivity or structural characterizations within the DMN were able to predict individual creativity (Chen et al., 2015; Takeuchi et al., 2012; Wei et al., 2014). Thus the DMN activity contributes to the spontaneous generation of candidate ideas, which was considered as an initial and vital phase during creative thinking process. The control network and attention networks, on the other hand, have been shown to be responsible for the evaluation of candidate ideas during creative cognitive processes (Dietrich, 2004; Dietrich and Kanso, 2010). As a further step, our findings highlight the importance of the interactions among high level cognitive control networks for creative thought processes. We found that the FCs between the DMN, control network and dorsal attention network/ventral attention network/memory retrieval network correlate positively with the TTCT score. Our results suggest that creative thinking involves the free generation of possible solutions as well as selection among the produced alternatives (Campbell, 1960), that arise from the default mode network (DMN) and executive control networks, respectively (Dietrich A and R Kanso 2010; Beaty RE et al. 2016). More importantly, these results provide support for the hypothesis that creative thought benefits from dynamic cooperation of the default mode and control networks to produce thoughts that are both novel and appropriate. Thus,

creative ideas depend on self-generated thought but also need control by a top-down goal-directed process (Beaty et al., 2016).

Our findings that the FCs between the DMN with the primary sensory networks (visual, auditory and sensory-motor) and ventral attention networks are negatively correlated with the individuals' creativity score, indicate that high creativity individuals have the ability to inhibit conspicuous task-relevant stimulation and shift toward task-irrelevant stimuli during creative thinking (Berkowitz and Ansari, 2010). This is in agreement with the finding that an individual's creativity level is positively related to increased alpha power in the frontal cortex during creative ideation, which reflects more internally orientated attention that is characterized by the absence of bottom-up stimulation (Fink and Benedek, 2014).

In addition to describing the creativity-related neural networks in terms of the few networks used by Power et al (Power et al., 2011), it is also useful to consider in more detail the brain areas related to the creativity score using a more detailed anatomical atlas such as a Brodmann parcellation (Jacobs, 2011). The MNI coordinates and Brodmann areas of the ROIs are shown in **Table S1** for the functional connectivities with positive correlations with figural creativity, and in **Table S2** for the functional connectivities with negative correlations with figural creativity.

First we focus on the functional connectivities with positive correlations with figural creativity shown in **Table S1** (see also **Table 1**). It is evident from **Table S1** that many (11) of the 44 areas involved in functional connectivity related to figural creativity involved left area BA 40 (part of Wernicke's area), or right BA 45, 46 and 47 (contralateral to Broca's area). Also related to this positive correlation with figural connectivity are the left inferior prefrontal convexity / lateral orbitofrontal cortex areas, which may relate to processing in the nearby Broca's area. Increased functional connectivity of some posterior cingulate areas (with e.g. temporal cortex areas) may reflect the involvement of these posterior cingulate areas in spatial processing (Kravitz et al., 2011) which is likely to be important for figural creativity. The findings described here are consistent with and thus supported by a meta-analysis of activations in 24 neuroimaging studies related to creativity (Boccia et al., 2015), but the functional connectivity analyses described here take the analysis an important step further, by providing evidence on which of the functional connectivities between these areas is related to figural creativity.

Second, we consider the functional connectivities with negative correlations with figural creativity shown in **Table S2** (see also **Table 1**). One brain area with prominent negative correlations was the fusiform gyrus, with its functional connectivities with an inferior frontal gyrus / lateral orbitofrontal cortex region (Power et. al. ROIs 175, 208, 211, and 198), with the anterior cingulate cortex (Power et. al. ROIs 216), and with the putamen especially marked (**Table S2**). The fusiform gyrus has perceptual

representations, and the inferior frontal gyrus on the left includes part of Broca's area and also non-reward / error systems (Rolls, 2016a; Rolls, 2016b). Another brain area with prominent negative correlations with figural creativity was the auditory cortex / supramarginal gyrus (Power et. al. ROIs 138) in especially its functional connectivities with secondary visual cortical areas (Power et. al. ROIs 164, 150, 173, 151, V3, V4 and V5). The reduced functional connectivity between high order visual and auditory association cortical areas that is associated with high figural creativity might suggest that high figural creativity is associated with less visual/ auditory bottom-up processing.

Finally, the right hemisphere has been shown to play a dominant role in creative thinking (Bhattacharya and Petsche, 2005; Bowden and Jung-Beeman, 2003; Falcone and Loder, 1984; Friedman and Forster, 2005). It is interesting to note that although both within-hemisphere and between-hemisphere FCs correlate significantly with the figural creativity score, the 4 FCs that connect ROIs in the task control network and attention network, and the FC between the cingular-opercular control network and the memory retrieval network, are all right-lateralized. This suggests that increased top-down control in the right hemisphere facilitates a global thinking/context-dependent thinking style and figural processes crucial for figural creativity (Mihov et al., 2010).

The creativity of the brain may be related, at least partly, to genetic and environmental interactions (Blunt, 2010). Although the genetic causes of creativity may be diverse, many heterogeneous genes have been implicated in creativity such as those affecting DA, 5HT or GABA metabolism (Blunt, 2010; Reuter et al., 2006), mostly belonging to neuro-transmitter systems. It has been shown that reduced task-induced deactivation in the precuneus correlates with higher creativity in divergent thinking (Takeuchi et al., 2011). Considering also that individuals with a higher GABA/glutamate ratio tend to suppress ongoing neural activities of the precuneus more efficiently (Hu et al., 2013), these results indicate that the GABA/glutamate ratio may be closely related to the creativity of a brain.

Our genetic results are concordant with these findings by showing that mutations of genes related to both excitatory and inhibitory neurotransmitters are associated with creative thinking. We find that mutation of a SNP in GABRG3, the receptor for GABA, is negatively related to the figural TTCT score, while several SNPs in genes related to glutamate (SHANK2, FGF12) correlate positively with the figural TTCT score. The mutation of these SNPs relevant for neurotransmitter systems may disturb the balance between the two different kinds of neurotransmitter, i.e. glutamate and GABA. Since these mutations are found to be significantly associated with both the creativity-related network and the figural TTCT score, we therefore postulate that this difference in the glutamate and GABA transmitter may have an impact on the functional connectivity associated with regions (including the precuneus) of the DMN, control, and attention networks. Moreover, it is interesting to note that among all the 13 SNPs we found to be related to the figural TTCT score, 5 are associated with genes (ITGA4, SHANK2,

MIR548, GABRG3 and FGF12) that have been reported to be relevant to autism (Ander et al., 2015; Buxbaum et al., 2002; Correia et al., 2009; Leblond et al., 2012; Vaccarino et al., 2009; Won et al., 2012). Autistic traits have been demonstrated to be associated with high numbers of unusual responses on the divergent thinking tasks (Best et al., 2015).

In our feature selection and prediction procedures, we took into account factors that might have affected our prediction models. For example, for head motion, which could be a potential confounding factor for neuroimaging data, we performed two further motion control procedures in the 138 sample group to confirm that it did not confound our prediction models. Firstly, the correlation between the mean framewise displacement (FD) with the creativity score and our predicted score were calculated. We found that the mean FD did not correlate with the real TTCT score or the predicted score ($r = 0.116$, $p = 0.157$ and $r = 0.114$ and $p = 0.183$). Secondly, we used the brain network with the mean FD regressed out to build a new prediction model using the network strength of the creativity-related functional brain network. The correlation between the predicted score ($r = 0.420$) and the prediction accuracy (72.7%) did not differ significantly from the results provided in the Results section.

The relationship between the individuals' TTCT figural creativity and their age and Raven's score were also analyzed. The procedure was to use age, sex and the Raven's score as covariates in the regression equation (C_k in eq. 1 above) that estimated the creativity score from the Functional Connectivity. This ensured that the prediction was from the Functional Connectivity with the effects of age, sex and the Raven's score regressed out. We found that the figural creativity score was significantly though weakly ($p=0.037$) negatively related to age (from ~ 18 to ~22) (see **Fig. S4**). However, the Raven's score and sex were not significantly related to the figural creativity score, indicating that the figural creativity prediction is not confounded by individuals' gender or general intelligence (see **Fig. S5**). In the regression analysis, the coefficients for the neuroimaging data (part A) show that the coefficient for the average network strength made a contribution to the prediction that was significant at $p=6.19\times10^{-13}$, and that the coefficients for age, gender, and the Raven's score made no significant contribution to the prediction. In the Supplementary Material, in the prediction model from the genetic data (part B), there is a negative coefficient for the contribution of age that is significant ($p=1.92\times10^{-5}$), and this is of interest.

In conclusion, we have for the first time investigated both the neural and genetic correlates of figural creativity using whole-brain functional connectivity and the whole-genome. We find that we can predict figural connectivity significantly better from the functional connectivity and the genome (78.4%) than from the functional connectivity alone (76.1%) or the genetic data alone (77.5%). The FCs positively related to creativity were associated with the "control networks" and "attention networks" (as identified by Power et al (Power et al., 2011) typical of top-down processes, while the FCs negatively

related to creativity were between the default mode network (DMN) and the primary sensory networks that are associated with bottom-up processes. The implication is that figural creativity is associated with strong top-down control versus weak bottom-up process in the resting state. The genes associated with figural connectivity are involved in glutamate and GABA functionality, and an implication is that the ratio of excitatory to inhibitory synaptic function may be important in figural creativity. The results described here provides the first insight into how a combination of neural and gene-related factors are related to creative thinking. The brain areas related to figural creativity included increased visual association cortex connectivity with inferior frontal gyrus areas related to Broca's area, and with Wernicke's area, which may relate to enhanced visual imagery in those with high figural creativity.

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Table 1 Identified functional connectivities that are correlated with the TTCT figural score. As the 264 ROI template gives only the functional module that each ROI belongs to (rather than the names of exact brain region), in the following, we provide the names of the two functional modules for the two brain regions associated with each functional connectivity. Note that although the creativity-related functional connectivities are obtained by leave-one-out cross validation (i.e., the FCs common to each leave-one-out trial), the r and p value for the correlation are obtained using all 138 subjects. The network names used here are those used by Power et al. (Power et al., 2011). In the tables, ROI refers to the area in the Power et al atlas, and the Network name is the name that they used for the network of which this ROI is a part. R refers to the correlation value of the functional connectivity, and p to its significance.

(a) Functional connectivities that are correlated positively with the TTCT figural score

Shared positive creativity network.

ROI	Network	ROI	Network	R	P
208	Salience	73	Auditory	0.318	1.70E-04
53	Cingulo-opercular Task Control	235	Ventral attention	0.315	2.00E-04
29	Sensory/somatomotor Hand	132	Uncertain	0.308	2.82E-04
235	Ventral attention	264	Dorsal attention	0.308	2.85E-04
56	Cingulo-opercular Task Control	181	Fronto-parietal Task Control	0.302	3.77E-04
192	Fronto-parietal Task Control	161	Visual	0.298	4.55E-04
212	Salience	225	Subcortical	0.292	5.89E-04
235	Ventral attention	62	Auditory	0.290	6.59E-04
212	Salience	234	Subcortical	0.285	8.14E-04
197	Fronto-parietal Task Control	234	Subcortical	0.281	9.47E-04
235	Ventral attention	37	Sensory/somatomotor Hand	0.280	1.01E-03
48	Cingulo-opercular Task Control	264	Dorsal attention	0.276	1.18E-03

81	Default mode	91	Default mode	0.276	1.19E-03
124	Default mode	138	Ventral attention	0.276	1.20E-03
192	Fronto-parietal Task Control	151	Visual	0.272	1.42E-03
77	Default mode	250	Uncertain	0.268	1.64E-03
53	Cingulo-opercular Task Control	136	Memory retrieval	0.267	1.73E-03
186	Fronto-parietal Task Control	159	Visual	0.267	1.77E-03
97	Default mode	149	Visual	0.261	2.20E-03
182	Uncertain	204	Salience	0.258	2.48E-03
81	Default mode	88	Default mode	0.258	2.52E-03

(b) Functional connectivities that are correlated negatively with TTCT figural score

Shared negative creativity network					
ROI	**Network**	**ROI**	**Network**	**R**	**P**
49	Cingulo-opercular Task Control	149	Visual	-0.339	5.77E-05
91	Default mode	225	Subcortical	-0.339	5.80E-05
149	Visual	243	Cerebellar	-0.332	8.57E-05
216	Salience	253	Uncertain	-0.328	1.04E-04
91	Default mode	234	Subcortical	-0.325	1.19E-04
191	Fronto-parietal Task Control	227	Subcortical	-0.323	1.32E-04
138	Ventral attention	151	Visual	-0.320	1.54E-04

144	Visual	30	Sensory/somatomotor Hand	-0.318	1.76E-04
79	Default mode	235	Ventral attention	-0.317	1.83E-04
230	Subcortical	253	Uncertain	-0.311	2.46E-04
233	Subcortical	253	Uncertain	-0.310	2.53E-04
136	Memory retrieval	132	Uncertain	-0.309	2.61E-04
142	Uncertain	183	Uncertain	-0.305	3.27E-04
91	Default mode	224	Subcortical	-0.304	3.39E-04
126	Default mode	175	Fronto-parietal Task Control	-0.302	3.67E-04
208	Salience	253	Uncertain	-0.302	3.67E-04
77	Default mode	93	Default mode	-0.297	4.78E-04
101	Default mode	235	Ventral attention	-0.296	4.82E-04
53	Cingulo-opercular Task Control	151	Visual	-0.295	5.09E-04
53	Cingulo-opercular Task Control	245	Cerebellar	-0.295	5.20E-04
227	Subcortical	253	Uncertain	-0.292	5.98E-04
111	Default mode	235	Ventral attention	-0.290	6.44E-04
135	Memory retrieval	132	Uncertain	-0.289	6.79E-04
53	Cingulo-opercular Task Control	158	Visual	-0.288	7.09E-04
220	Salience	253	Uncertain	-0.288	7.23E-04
138	Ventral attention	150	Visual	-0.285	7.95E-04
86	Default mode	235	Ventral attention	-0.285	8.00E-04
138	Ventral attention	173	Visual	-0.283	8.78E-04

191	Fronto-parietal Task Control	228	Subcortical	-0.283	8.82E-04
125	Default mode	30	Sensory/somatomotor Hand	-0.283	8.95E-04
91	Default mode	73	Auditory	-0.282	9.37E-04
191	Fronto-parietal Task Control	233	Subcortical	-0.281	9.63E-04
91	Default mode	223	Subcortical	-0.280	1.02E-03
93	Default mode	19	Sensory/somatomotor Hand	-0.278	1.10E-03
228	Subcortical	253	Uncertain	-0.278	1.12E-03
234	Subcortical	253	Uncertain	-0.278	1.12E-03
138	Ventral attention	161	Visual	-0.277	1.16E-03
53	Cingulo-opercular Task Control	146	Visual	-0.276	1.19E-03
92	Default mode	121	Default mode	-0.276	1.22E-03
227	Subcortical	31	Sensory/somatomotor Hand	-0.273	1.36E-03
67	Auditory	8	Uncertain	-0.272	1.41E-03
133	Memory retrieval	224	Subcortical	-0.271	1.47E-03
218	Salience	219	Salience	-0.270	1.54E-03
138	Ventral attention	164	Visual	-0.270	1.56E-03
211	Salience	253	Uncertain	-0.269	1.59E-03
198	Fronto-parietal Task Control	253	Uncertain	-0.268	1.67E-03
77	Default mode	163	Visual	-0.267	1.76E-03
80	Default mode	132	Uncertain	-0.267	1.77E-03
237	Ventral attention	241	Ventral attention	-0.267	1.77E-03

175	Fronto-parietal Task Control	226	Subcortical	-0.266	1.80E-03
144	Visual	132	Uncertain	-0.266	1.80E-03
1	Uncertain	183	Uncertain	-0.266	1.80E-03
91	Default mode	61	Auditory	-0.266	1.82E-03
145	Visual	250	Uncertain	-0.266	1.83E-03
82	Default mode	235	Ventral attention	-0.265	1.89E-03
151	Visual	169	Visual	-0.264	1.96E-03
82	Default mode	130	Default mode	-0.264	1.99E-03
78	Default mode	225	Subcortical	-0.263	2.05E-03
161	Visual	35	Sensory/somatomotor Hand	-0.262	2.18E-03
133	Memory retrieval	223	Subcortical	-0.260	2.36E-03

Table 2 Identified SNPS whose mutations are correlated with the TTCT figural score

(a) positive correlation

Shared positive polygenic alliance		
SNP id	**gene name**	**single SNP p_value**
rs4631724	COL24A1	8.84E-06
rs9877993	FGF12	3.97E-06
rs4455277	MB21D2	6.34E-06
rs2082400	SLIT3	1.77E-05
rs9486484	NA	1.00E-05
rs17788018	MIR548Q	3.12E-05
rs11021924	GALNT18	2.25E-05
rs4340077	SHANK2	2.72E-05

(b) negative correlation

Shared negative polygenic alliance		
SNP id	**gene name**	**single SNP p_value**
rs200693221	ITGA4	1.01E-06
rs77555152	CERKL	3.42E-06
rs7718883	SLIT3	2.80E-06
rs6984541	NA	4.64E-06
rs6606905	GABRG3	2.75E-05

* NA represents the SNP is not in the coding gene region

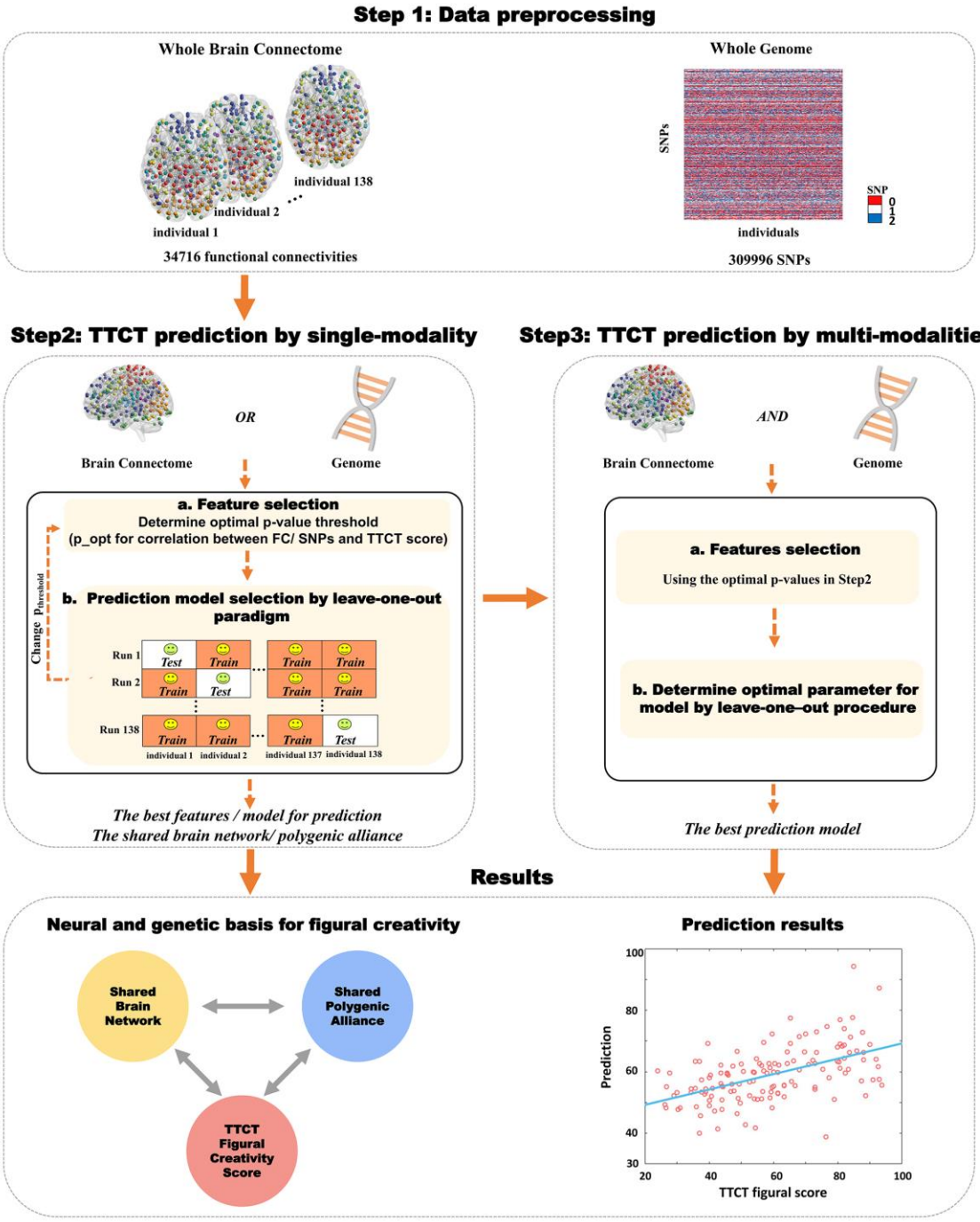

Fig 1. Flowchart for predictions of the individual creativity score using whole brain functional-connectivity and genome information.

Step 1: Data preprocessing: A functional network with 264 nodes is constructed with the resting state fMRI data for each individual. Different colors represent the node in different networks such as the DMN and control network etc. Whole genome SNPs were also identified for each individual. **Step 2**: TTCT creativity score prediction by unimodal data. (a) First we set a threshold of p values for the correlation between functional connectivity/mutations of SNPS and TTCT score, and only FCs or SNPs with $p < p_{threshold}$ are selected. (b) We then use a linear regression model and leave-one-

out paradigm to predict TTCT score of each individual. We change $p_{threshold}$ to select the optimal one (p_opt) that achieves the best prediction. **Step 3**: TTCT creativity score prediction by multimodal data. We integrate fMRI and genome data in an elastic network in predicting the TTCT score, using the optimal $p_{threshold}$ identified in Step 2. **Results**: (a) shows the correlation between the Shared networks, shared SNPs, and TTCT score obtained in Step 2 and (b) shows the correlation between the predicted TTCT score and real score of the individuals.

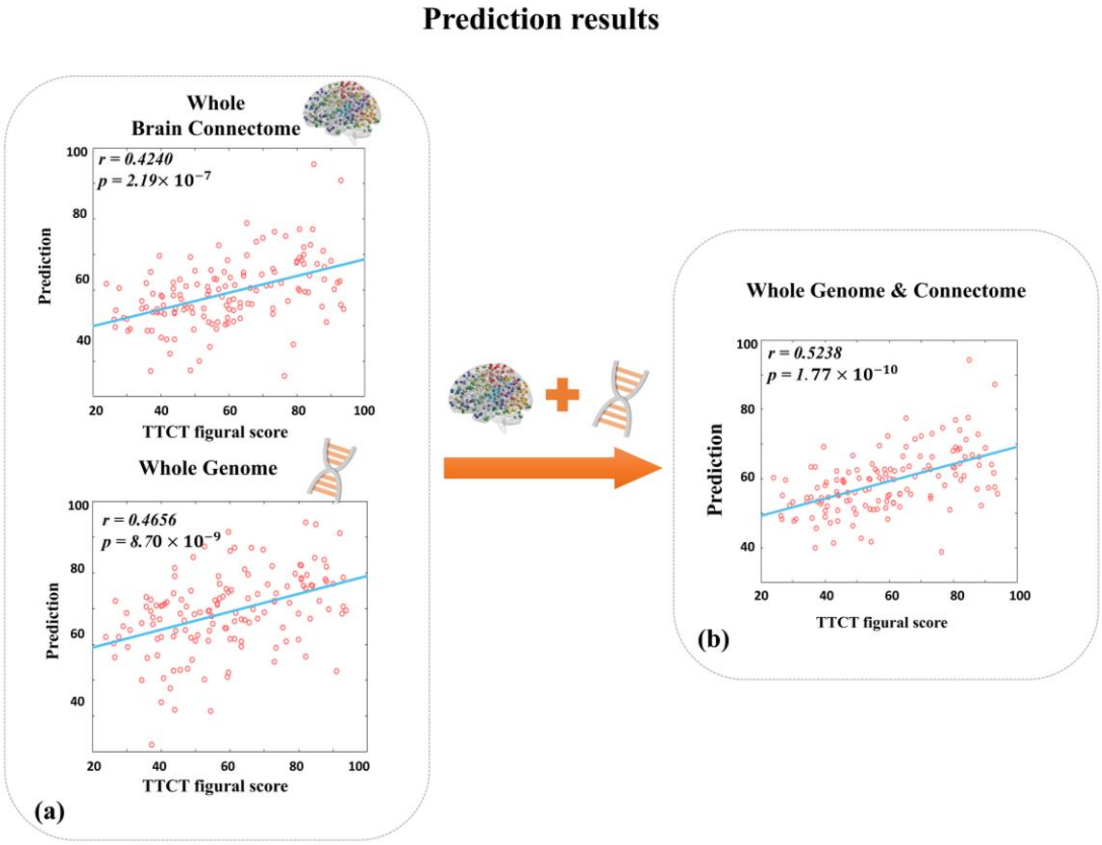

Fig 2. The results of predicting an individual's TTCT creativity score.
(a) The results of predicting an individual's TTCT creativity score using whole genome/connectome data. **(b)** The results of predicting an individual's TTCT creativity score combining whole-genome/connectome data. Here the scatter plot between the predicted TTCT creativity score of each individual and the real TTCT score is plotted.

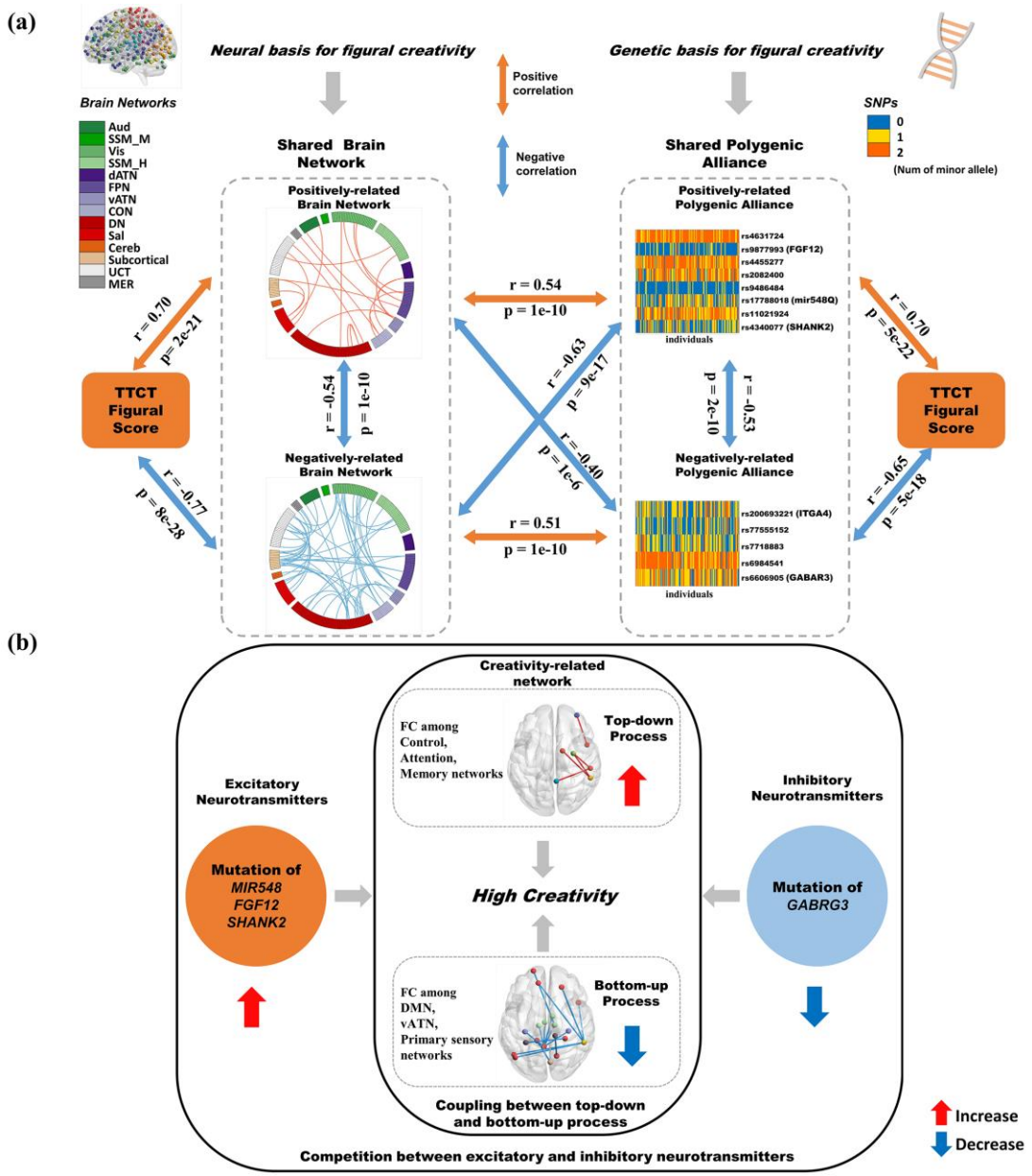

Fig 3. Summary of the neural and genetic basis for figural creativity.

(a) The neural and genetic basis for figural creativity. The shared positively /negatively-related FCs (with the TTCT score) are shown by red and blue on the left. Different sub-networks are represented by different colors in the left legend. The mutation of the shared positively-related/negatively-related (with the TTCT score) polygenic alliance are shown on the right, each row representing a SNP and each column represents an individual. Different colors denote different numbers of the minor allele. The correlations within/between the network strength of the shared positive/negative network and mutation strength of the shared positive/negative creativity polygenic alliance are shown in **(a)**, as well as their correlation with the TTCT figural score. **(b)** The creativity model we presented. The inner rectangle shows that both the increased top-down processing (in red arrows) and the decreasing bottom-up processing (in blue)

relate to high creativity. The corresponding FCs relevant for top-down/ bottom-up processing are also shown. The outer rectangle demonstrates the genetic factors contributing to high creativity. The mutation strength of the excitatory neurotransmitter related genes increases with creativity, and the mutation strength of the inhibitory neurotransmitter related genes decreases with creativity. The competition between the two different kinds of neurotransmitters may influence the brain activity and further contribute to the high creativity.